REMARKS

Status of the Claims

Claims 48-91 are pending in the application.

Claims 48-91 remain under consideration with entry of this amendment.

Summary

Claims 48-91 are pending in the application and were examined in the Office Action dated 23 June 2005. In the Action, the specification has been objected to as informal. In addition, the following claim rejections have been raised: **(a)** claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,541,021; **(b)** claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,689,373; **(c)** claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over U.S. Patent No. 6,835,194; **(d)** claims 48-91 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over co-pending U.S. Application Serial No. 11/044,521; **(e)** claims 48-91 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 4,210,139 to Higuchi ("Higuchi") in view of U.S. Patent No. 5,980,927 to Nelson et al. ("Nelson"); and **(f)** claims 48-91 stand rejected under 35 U.S.C. §103(a) as unpatentable over U.S. Patent No. 6,287,295 to Chen et al. ("Chen") in view of Nelson. Applicants respectfully traverse all pending claim rejections for the following reasons.

Overview of the Amendment

Applicants, by way of this amendment, have amended the specification in order to recite updated priority entitlement from the parent applications. Accordingly, entry of the subject amendment is respectfully requested.

Accompanying Documents

Accompanying this Response are the following documents:

- A Terminal Disclaimer over commonly owned U.S. Patent No. 6,541,021, with associated 37 C.F.R. §3.73(b) Statements.
- A Terminal Disclaimer over commonly owned U.S. Patent No. 6,689,373, with associated 37 C.F.R. §3.73(b) Statements.
- A Terminal Disclaimer over commonly owned U.S. Patent No. 6,835,194, with associated 37 C.F.R. §3.73(b) Statements.

The Objection to the Specification

The specification was objected to on the basis that applicants' priority claim/reference to prior applications was missing from the application. In response, applicants have tendered herewith an amendment to the specification to supply the missing information.

The Obviousness-type Double Patenting Rejections

Claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-23 and 34-63 of U.S. Patent No. 6,541,021. This is a non-statutory double patenting rejection. Without acquiescing to any stated grounds for the rejection, applicants have submitted herewith a Terminal Disclaimer over U.S. Patent No. 6,541,021. A timely filed terminal disclaimer may be used to overcome a non-statutory double patenting rejection provided that the conflicting patent is commonly owned with the present application, and applicants confirm that this is the case. Accordingly, applicants respectfully request that the Office accept the Terminal Disclaimer submitted herewith and withdraw the rejection of claims 48-91 under the judicially created doctrine of obviousness-type double patenting.

Claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-15 of U.S. Patent No. 6,689,373. This is a non-statutory double patenting rejection. Without acquiescing to any stated grounds for the rejection, applicants have submitted herewith a Terminal Disclaimer over U.S. Patent No.

6,689,373. A timely filed terminal disclaimer may be used to overcome a non-statutory double patenting rejection provided that the conflicting patent is commonly owned with the present application, and applicants confirm that this is the case. Accordingly, applicants respectfully request that the Office accept the Terminal Disclaimer submitted herewith and withdraw the rejection of claims 48-91 under the judicially created doctrine of obviousness-type double patenting.

Claims 48-91 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 10-17 and 24-27 of U.S. Patent No. 6,835,194. This is a non-statutory double patenting rejection. Without acquiescing to any stated grounds for the rejection, applicants have submitted herewith a Terminal Disclaimer over U.S. Patent No. 6,835,194. A timely filed terminal disclaimer may be used to overcome a non-statutory double patenting rejection provided that the conflicting patent is commonly owned with the present application, and applicants confirm that this is the case. Accordingly, applicants respectfully request that the Office accept the Terminal Disclaimer submitted herewith and withdraw the rejection of claims 48-91 under the judicially created doctrine of obviousness-type double patenting.

Claims 48-91 have been provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-36 of copending U.S. Application Serial No. 11/044,521. This is a provisional rejection, and applicants respectfully ask that the rejection be held in abeyance until the subject rejection is the only one remaining in either the present application or in the 11/044,521 application.

The Rejections under 35 U.S.C. §103

Claims 48-91 stand rejected under 35 U.S.C. §103(a) as unpatentable over Higuchi in view of Nelson. In essence, the Office asserts: (a) Higuchi teaches an osmotic device for controlled delivery, that is also implantable; and (b) although Higuchi fails to teach delivery of fentanyl, nor its amount, nor its delivery rates, Nelson teaches continuous administration of analgesics from an implantable device, where fentanyl is preferred. The Office then concludes "the amount and delivery rate of the active agent do

not impart patentability, absent evidence to the contrary. Office Action at page 6. Applicants respectively traverse the rejection.

When considering the patentability of claims under Section 103, the claimed invention must be considered as a whole, the reference(s) must be considered as a whole and must suggest the desirability and thus the obviousness of making the combination, the reference(s) must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention; and a reasonable expectation of success is the standard with which obviousness is determined. *Hodosh v. Block Drug Co., Inc.*, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986). Therefore, it is clear that in order to establish obviousness, the cited prior art must enable a person of ordinary skill to make and use the invention (*see: In re Kumar*, CAFC 04-1074, (decided 15 August 2005) and *Beckman Instruments, Inc. v. LKB Produkter AB*, 892 F.2d 1547 (Fed. Cir. 1989); *see also: Motorola, Inc. v. Interdigital Tech. Corp.*, 121 F.3d 1461 (Fed. Cir. 1997); and *In re Payne*, 606 F.2d 303 (CCPA 1979), and that a two-part test must be used to assess obviousness--where an appropriate teaching or suggestion must first be found in the prior art itself, and then a proper consideration must be made to assess whether or not the prior art actually enables the recited subject matter.

Claim 48 requires a composition wherein, upon administration, the fentanyl or fentanyl congener is delivered from the system at a very low volume rate (2 ml/day or less) and still provides sufficient analgesia in the subject. Claims 49-62 each depend, either directly or indirectly from claim 48 and thus contain these same base limitations. Claim 63 requires a composition wherein the fentanyl or fentanyl congener is present in exceptionally high concentration (from 0.5 mg/ml to 500 mg/ml or greater) and, upon administration, the fentanyl or fentanyl congener is delivered from the system at a very low volume rate (2 ml/day or less) and still provides sufficient analgesia in the subject. Claims 64-83 each depend, either directly or indirectly from claim 63 and thus contain these same base limitations. Claim 84 requires a composition wherein, upon administration, the fentanyl or fentanyl congener is delivered from the system at a very low volume rate sufficient to deliver from 0.01 to 200 μg/hour of the active agent and

still provide sufficient analgesia in the subject. Claims 85-91 each depend, either directly or indirectly from claim 84 and thus contain these same base limitations.

Accordingly, each of claims 48-91 can be characterized as methods where an exceptionally small volume of a composition containing the fentanyl/fentanyl congener active agent is delivered, yet the methods are nonetheless able to achieve therapeutically effective analgesia in the subject. These requirements are absolutely counter-intuitive, in that one would logically expect that the efficacy of drug administration would quickly drop off and become negligible well before one reached the low volume rate delivery as required by applicants' claims. This would have been particularly counter-intuitive to the ordinarily skilled person, operating in the field of pharmacology and in particular in the field of pain management using fentanyl or fentanyl congeners prior to applicants' priority date (March 1999). This is because it was widely believed at the time of applicants' invention that the solution to the logical riddle outlined above—that is, that one would need to create an exceptionally high concentration fentanyl/fentanyl congener formulation that could be delivered at very low volume rates—was simply unattainable. As disclosed in applicants' specification, the fentanyl/fentanyl congener is present in the formulations of the invention in a concentration substantially higher than conventional formulations, in fact, the active agent can be present in up to 10,000 times or greater than the solubility of the fentanyl or fentanyl congener in aqueous solution. See applicants' specification at page 18, second full paragraph through page 21, first full paragraph. Working examples where fentanyl congener formulations of 397 mg/ml, 310 mg/ml, 248 mg/ml and 77 mg/ml are provided in applicants' specification at pages 35 and 36 (Examples 3 and 4).

It was surprising and heretofore unheard of to produce such high concentration fentanyl/fentanyl congener formulations prior to applicants' priority date. Applicants' ability to produce such formulations provided exceptional benefit to the art in that now, methods of pain management can be carried out by administering exceptionally small volumes of the fentanyl/fentanyl congener formulation to a site, avoiding accumulation of excessive drug at the delivery site (pooling or depot effect) since the rate of

administration is at or only slightly higher than the rate of removal of the drug from the delivery site. See applicants specification at page 24, bottom paragraph.

None of the above-described features can be found in the cited art. Higuchi is related to the claimed invention on the sole basis that it describes an osmotic pump drug delivery system. Higuchi never taught or suggested that very high concentration fentanyl/fentanyl congener formulations could be delivered from such a device. Nelson describes the production of solid implant systems, where a particulate analgesic (e.g., fentanyl powder) is added to a solvated polymer (polyurethane) and then dried to produce a solid (film). See Nelson, column 7, lines 7-18 and lines 34-49. Accordingly, the assertion that one could simply combine Nelson's dried solid with the osmotic pump of Higuchi and arrive at a system that is able to deliver low volumes of a fentanyl/fentanyl congener formulation to provide therapeutically effective doses of the analgesic is entirely incorrect. The Higuchi osmotic pump obviously delivers a liquid formulation, and one simply cannot substitute a solid film in that pump, it just would not operate. In addition, the skilled person did not know that one could produce fentanyl/fentanyl congener formulations of a high enough concentration to facilitate applicants' efficacious low volume delivery rates. When the test of obviousness is thus applied to these facts, it is clear that applicants' recited methods are not obvious over the combination of Higuchi and Nelson. The devices of Higuchi and Nelson are simply not combinable or interchangeable. Higuchi never taught nor suggested delivery of low volumes of a high concentration fentanyl/fentanyl congener formulation, and the skilled person did not think that such formulations were attainable. Without even one, much less all of these essential elements, applicants' invention was simply not obvious. In addition, in the absence of these essential elements, it simply cannot be argued that applicants' recited methods were sufficiently enabled by the recited art.

For all of the foregoing reasons, then, the rejection of claims 48-91 under 35 U.S.C. §103(a) over the combination of Higuchi and Nelson is incorrect. Reconsideration and withdrawal of the rejection is thus earnestly solicited.

Claims 48-91 stand rejected under 35 U.S.C. §103(a) as unpatentable over Chen in view of Nelson. In essence, the Office asserts: (a) Chen teaches an osmotic device for

controlled delivery, that is also implantable; and (b) although Chen fails to teach delivery of fentanyl, nor its amount, nor its delivery rates, Nelson teaches continuous administration of analgesics from an implantable device, where fentanyl is preferred. The Office then concludes "the amount and delivery rate of the active agent do not impart patentability, absent evidence to the contrary. Office Action at page 7. Applicants respectively traverse the rejection.

Applicants note that this present rejection is substantially identical to the previous rejection over Higuchi and Nelson, where the primary (Chen) reference has been substituted for the previous primary (Higuchi) reference. Applicants have discussed the scope of the various claims series of claims 48-91 herein above, and will not repeat the same. In addition, applicants have provided a detailed traversal regarding the state of the cited art in this case, and how their recited invention departs from the respective teachings.

In regard to the present rejection, none of the essential features of applicants' recited invention (low volume delivery of fentanyl/fentanyl congeners to provide effective analgesia, production and use of exceptionally high concentration formulations) can be found in the cited art. Chen is related to the claimed invention on the sole basis that it describes an osmotic pump drug delivery system. Chen never taught or suggested that very high concentration fentanyl/fentanyl congener formulations could be delivered from such a device. The passage from Chen that the Office has identified (column 19, line 3) merely recites "analgesic" as part of a laundry list of potential agents that spans more that an entire column. There is simply nothing from Chen that could be argued to be an enabling disclosure that high concentration fentanyl/fentanyl congener formulations could in fact be made, and then delivered at exceptionally low volume delivery rates to provide effective analgesia.

As discussed above, Nelson merely describes the production of solid implant systems. Accordingly, an assertion that one could simply combine Nelson's dried solid with the osmotic pump of Chen and arrive at a system that is able to deliver low volumes of a fentanyl/fentanyl congener formulation to provide therapeutically effective doses of the analgesic is entirely incorrect. Just as with the Higuchi system, Chen's osmotic pump

obviously delivers a liquid formulation, and one simply cannot substitute a solid film in that pump, it just would not operate. In addition, the skilled person did not know that one could produce fentanyl/fentanyl congener formulations of a high enough concentration to facilitate applicants' efficacious low volume delivery rates. When the test of obviousness is thus applied to these facts, it is clear that applicants' recited methods are not obvious over the combination of Chen and Nelson. The devices of Chen and Nelson are simply not combinable or interchangeable. Chen never taught nor suggested delivery of low volumes of a high concentration fentanyl/fentanyl congener formulation, and the skilled person did not think that such formulations were attainable. Without even one, much less all of these essential elements, applicants' invention was simply not obvious. In addition, in the absence of these essential elements, it simply cannot be argued that applicants' recited methods were sufficiently enabled by the recited art.

CONCLUSION

Applicants submit that the pending claims define an invention that is both novel and nonobvious over the cited art, and thus all claims are in condition for allowance. Acknowledgement of this by the Office in the form of an early allowance is thus respectfully requested. In addition, if the Examiner contemplates other action, or if a telephone conference would expedite allowance of the claims, applicants invite the Examiner to contact the undersigned at (408) 777-4915. However, applicants ask that the Examiner kindly continue to use the following correspondence address for all future written communications:

Bozicevic, Field & Francis LLP
1900 University Avenue
Suite 200
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Applicants believe that the appropriate fees have been attached hereto. However, if the Commissioner determines that an additional fee is indeed necessary, the Commissioner is hereby authorized to charge any additional fees associated with this communication to Deposit Account No. **50-1953.**

Respectfully submitted,

Date: 21 December 2005

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